IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of: | Istvan BAKONDI-KOVACS *et al.* |
| Application No.: | 10/047,693 |
| Filed: | January 9, 2002 |
| For: | METABOLIC CONTROLLED FERMENTATION PROCESS FOR CARBAMOYL TOBRAMYCIN PRODUCTION |
| Examiner: | MARX, Irene |
| Art Unit: | 1651 |
| Docket No. | 02664/47002 |

**Mail Stop AF**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Sir:

Applicants requests review of the final rejections in the above-identified application for the reasons stated on the attached five (5) sheets.

No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

Respectfully Submitted,

Dated: March 7, 2006

King L. Wong
King L. Wong
Reg. No. 37,500

Attachment: Reasons in Support of Pre-Appeal Brief Request for Review

KENYON & KENYON LLP
1500 K Street, N.W., #700
Washington, DC 20005
202-220-4200 (phone)
202-220-4201 (facsimile)

## REASONS IN SUPPORT OF PRE-APPEAL BRIEF REQUEST FOR REVIEW

The Examiner failed to show *prima facie* obviousness of claims 1-27 over Ott *et al.* taken with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre *et al.*

Ott *et al.* discloses a batch-mode fermentation process for producing 6'-O-carbamoyl tobramycin by incubating a medium containing a 6'-O-carbamoyl tobramycin producing strain MNG204 of *Streptomyces tenebrarius*, and organic carbon and nitrogen sources in a submerged, aerated culture until a substantial amount of 6'-O-carbamoyl tobramycin is accumulated (page 2, lines 27-38; page 3, lines 4, 5 and 14; page 4, line 15).

Tomita *et al.* also discloses a batch-mode fermentation process for producing 6'-O-carbamoyl tobramycin by culturing a strain of 6'-O-carbamoyl tobramycin producing *Streptoalloteichus hindustanus* in a medium containing assimilable sources of carbon and nitrogen (col. 10, line 64 to col. 11, line 5; col. 11, lines 32-37 and col. 14, lines 43-53).

Ott *et al.* and Tomita *et al.* differ from claims 1-27 at least in not teaching or suggesting regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth containing the 6'-O-carbamoyl tobramycin producing microorganism, the assimilable carbon source and the assimilable nitrogen source. The secondary references fail to cure this deficiency of Ott *et al.* and Tomita *et al.*

The Examiner relied on the secondary references, BG 50996, Vanek *et al.* and McIntyre *et al.*, "only for their disclosure of the knowledge in the art of the use of regulating constant levels of assimilable carbon and nitrogen sources" (page 3, first paragraph, Final Office Action of September 7, 2005). But applicants note that the secondary references do not disclose that "the use of regulating constant levels of assimilable carbon and nitrogen sources" was known.

BG 50996 does not disclose regulating constant levels of assimilable carbon and nitrogen sources because BG 50996 discloses a batch-mode fermentation method to prepare tobramycin. In response to Examiner's request, applicants do not have an English translation of BG 50996.

Vanek *et al.* does not suggest regulating constant levels of the assimilable carbon source and assimilable nitrogen source in a fermentation broth containing a 6'-O-carbamoyl tobramycin producing microorganism. Just because Vanek *et al.* discloses the potential use of chemostats does not necessarily mean that a person of ordinary skill in the art would have been motivated to modify the processes of Ott *et al.* and Tomita *et al.* by using a chemostat. Vanek *et al.* merely teaches **using chemostats to select certain mutants** of the microorganism growing in a

fermentation medium, wherein the selection is obtained by a constant feed of a known nutrient, which is lactose (please see the section title, "IV. Selection and Accumulation in Open Systems" in page 191; page 191, the last two paragraphs; page 192, the last three paragraphs; Figure 9.1 in page 193; page 195, the first 3 paragraphs). But Ott *et al.* and Tomita *et al.* do not teach or suggest the desirability of selecting certain mutants of the 6'-O-carbamoyl tobramycin producing microorganisms growing in the fermentation media. Thus, there would have been no suggestion or motivation to modify the processes of Ott *et al.* and Tomita *et al.* by using the chemostat process of Vanek *et al.* to select certain mutants of the microorganisms, let alone using the chemostat of Vanek *et al.* to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation broth.

Even if, *arguendo*, the person of ordinary skill in the art were to attempt to select certain mutants of the 6'-O-carbamoyl tobramycin producing microorganisms in the processes of Ott *et al.* and Tomita *et al.*, the person would not have been motivated to use the chemostat process of Vanek *et al.* because there would have been no reasonable expectation of success. The person would not have reasonably expected that attempting to select certain mutants in the 6'-O-carbamoyl tobramycin producing microorganisms used in the processes of Ott *et al.* and Tomita *et al.* would work, and be desirable. There was no reasonable expectation that the mutant selection would work with the 6'-O-carbamoyl tobramycin producing microorganisms used in the processes of Ott *et al.* and Tomita *et al.* because there was no teaching of whether the 6'-O-carbamoyl tobramycin producing microorganisms used in the processes of Ott *et al.* and Tomita *et al.* have auxotrophic mutants and prototrophic parent strains, or constitutive mutants and hyperproducing mutants, to allow for mutant selection to be achieved. Even if, for argument purposes, that one were to assume that the mutant selection would work, there was no reasonable expectation that the mutant selection would be beneficial to the production of 6'-O-carbamoyl tobramycin. With a lack of reasonable expectation of success, there would have no motivation to use the chemostat of Vanek *et al.* to modify the processes of Ott *et al.* and Tomita *et al.*

Applicants also note that, even if the person were to use the chemostat process of Vanek *et al.* to modify the processes of Ott *et al.* and Tomita *et al.* in an attempt to select certain mutants of the 6'-O-carbamoyl tobramycin producing microorganisms used in the processes of Ott *et al.* and Tomita *et al.*, the person would not have achieved the claimed process of the instant application because the chemostat process of Vanek *et al.* feeds a constant level of only lactose, not regulating a constant level of an assimilable nitrogen source.

Applicants disagree with the Examiner's allegation that "the Bulgarian patent '996 and McIntyre et al. adequately demonstrate the use of regulation of carbon and nitrogen sources in the production of antibiotics with *Streptomyces*, respectively *S. tenebrarius* strains using a constant glucose and nitrogen feed...". As pointed out above, BG 50996 uses a batch-mode fermentation process. The paragraph bridging the left and right columns in page 2 of McIntyre *et al.* merely discloses the general procedures for incubation of production flasks, and is silent on regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth containing the 6'-O-carbamoyl tobramycin producing microorganism, an assimilable carbon source and an assimilable nitrogen source.

McIntyre *et al.* shows the production of vancomycin by *Amycolatopsis orientalis* cultures with constant feed of glucose (Fig. 5). But McIntyre *et al.* does not teach regulating a constant level of assimilable nitrogen source in the fermentation broth. Thus, even if the person of ordinary skill in the art were to use the disclosures of McIntyre *et al.* to modify the fermentation processes of Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.* and BG 50996, the person would not have arrived at the process of claim 1.

The Final Office Action asserts that McIntyre *et al.* strongly suggests that feeding nitrogen would be appropriate because McIntyre *et al.* states at page 415, last paragraph, that "growth had ceased due to nitrogen limitation." Applicants emphasize that McIntyre *et al.* does not suggest that feeding nitrogen would be appropriate in a continuous-feed culture because page 415, last paragraph, of McIntyre *et al.* refers only to batch-mode cultures of *A. orientalis*.

Page 3 of the Final Office Action erroneously alleges that there is no clear indication in the instant application that the level of the assimilable nitrogen source is maintained constant. Actually, there was depletion of the nitrogen source only in the comparative Examples 1-3 conducted in batch mode (p. 11, lines 6 and 23). But the levels of the nitrogen source were maintained constant in working Examples 4-5 (p. 12, lines 15-17; page 13, lines 6-9).

Page 4, lines 1-3, of the Final Office Action states that regulation at constant levels would be reasonably expected at the time of depletion of nutrients. But applicants note that, at time of nutrient depletion, no improved yield of 6'-O-carbamoyl tobramycin would be expected.

Even if, *arguendo*, one were to assume that following the continuous culture process of Fig. 5 of McIntyre *et al.* would regulate a constant level of assimilable nitrogen source, Fig. 5 of McIntyre *et al.* deals with the production of **vancomycin, not 6'-O-carbamoyl tobramycin**. McIntyre *et al.* admits that the physiological regulation and control of the production of

antibiotics in *Streptomyces* is poorly understood (see p. 412, right column, the first sentence of the first full paragraph). According to McIntyre *et al.*, the production of antibiotics by microorganisms is not reasonably predictable (McIntyre, p. 412, right column, second and third sentences of the first full paragraph). There was no reasonable expectation that applying the teachings of McIntyre *et al.* on the production of **vancomycin** using a continuous culture process to modify the processes of Ott et al and Tomita et al would improve the production of another antibiotic, namely **6'-O-carbamoyl tobramycin**, compared with the batch-mode processes of Ott et al and Tomita et al.

Another reason why claims 1-27 would not have been *prima facie* obvious over Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre is that the prior art does not teach that modifying the processes of Ott *et al.* and Tomita *et al.* by using the chemostat of Vanek *et al.*, the batch-mode process of BG 50996, or the continuous culture process of McIntyre *et al.* to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation broth would result in an **improved yield** of the 6'-O-carbamoyl tobramycin as required by step b) of claim 1.

Page 4 of the Final Office Action states that the claims do not recite the level of the improved yield. Applicants note that the claims cover a process for producing 6'-O-carbamoyl tobramycin that achieves improved yield by regulating constant levels of the carbon and nitrogen sources in the broth. Examples 4-5 showed improved yields by over 40%. The prior art cited by the Examiner does not teach a motivation of regulating the constant levels to achieve improved yields of 6'-O-carbamoyl tobramycin.

Applicants note that McIntyre *et al.* discloses that "[d]espite the potential of increased volumetric productivity compared to batch culture, continuous culture processes have not been employed in commercial antibiotic production, primarily as a result of strain degeneration leading to lower productivity" (see p. 412, right column, second full paragraph, second sentence). McIntyre *et al.* also discloses that "**[d]ecreases** in antibiotic production under various nutrient and growth conditions in continuous culture studies have **frequently** been reported for *Streptomyces*" (p. 418, left column, first full paragraph, second sentence; emphasis added). Thus, McIntyre *et al.* **teaches away** from modifying the 6'-O-carbamoyl tobramycin production processes of Ott et al and Tomita et al using the continuous culture procedure.

In addition, applicants note that McIntyre *et al.* teaches the use of the continuous culture procedure as **a means of researching** the relationship between the physiological status of an

organism and the production of antibiotics under steady-state culture conditions (see p. 412, right column, second full paragraph, the third sentence; emphasis added). There would have been no motivation to modify a prior art substance if the prior art does not teach any specific or significant utility for the prior art substance. *See In re Stemniski*, 170 USPQ 343 (CCPA 1971); *In re Lalu*, 223 USPQ 1257 (Fed. Cir. 1984). According to MPEP 2107.01, carrying out further research to identify or reasonably confirm a "real world" context of use is not "substantial utility." Thus, there would have been no motivation to apply the continuous culture procedure taught by McIntyre *et al.* as a means of research in the process of Ott *et al.* taken with Tomita *et al.*, Vanek *et al.* and BG 50996.

Due to at least the reasons discussed above, claims 1-27 would not have been *prima facie* obvious over Ott *et al.* taken with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre *et al.*